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| <b>(54) Title: METHOD FOR THE TREATMENT OF RESPIRATORY DISEASE</b>   |  |   |  |
| <b>(57) Abstract</b>   |  |   |  |
| <p>A method of treating patients suffering from a respiratory disease using a programmable, handheld, self-contained drug dispensing device (1) is disclosed. The drug dispensing device is comprised of a container (3) which includes a formulation (4) comprised of a respiratory drug enzyme and a suitable propellant which is generally in the form of a low boiling point propellant combined with an excipient which facilitates the suspension of the drug within the propellant. The drug dispensing device (1) is designed such that when a patient withdraws air from a mouthpiece (12) on the device (1), the patient's inspiratory flow is measured (15) and analyzed in terms of liters per minute as well as cumulative inspiratory volume in order to provide an inspiratory profile which can be used to calculate an optimal point for the release (25, 26) of drug from the dispensing device (1).</p> |  |   |  |
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## METHOD FOR THE TREATMENT OF RESPIRATORY DISEASE

Field of the Invention

This invention relates generally to methods of 10 treating humans suffering from a respiratory disease. More specifically, this invention relates to the controlled interpulmonary delivery of respiratory drugs including anti-inflammatory drugs, bronchodilators and enzymes for the treatment of respiratory disease.

15

Background of the Invention

Asthma is a disease effecting approximately 20 million Americans. The death rates from asthma have increased substantially since 1979, increasing for 20 children over five years of age from the period from 1979 to 1982. Hospitalization rates for asthma increased by 50% for adults and by over 200% for the period from 1965 to 1983. Hospitalization rates for black patients are 50% higher for adults and 150% higher for children.

25 (R. Evans et al., "National Trends in the Morbidity and Mortality of Asthma in the US," *Chest* (1987) 91(6) Sup., 65S-74S). Increasing asthma mortality rates for the same period of time has been documented in other countries.

30 (R. Jackson et al., "International Trends in Asthma Mortality: 1970-1985," *Chest* (1988) 94, 914-19.)

The mainstay for the management of asthma as well as other respiratory diseases in the United States has been inhaled aerosolized medication. The primary aerosolized drugs currently prescribed for respiratory 35 therapy in the United States are anti-inflammatory drugs,

bronchodilators and enzymes. These medications can be self-administered by patients using hand held metered dose inhalers (MDIs). Bronchodilators, while useful for the management of an acute asthma attack, are currently 5 not the preferred drugs of choice for long-term asthma management. Aerosolized anti-inflammatory drugs, such as inhaled steroids and cromoglycates, used in conjunction with objective measures of therapeutic outcome are the preferred tools for long-term management of the asthmatic 10 patient. (U.S. Department of Health and Human Services, "Guidelines for the Diagnosis and Management of Asthma," *National Asthma Education Program Expert Panel Report*, pub. no. 91-3042, August 1991.)

Quantitative spirometry allows clinically 15 relevant indices of pulmonary function to be followed in the asthmatic patient during therapy or for any patient suffering from a respiratory disease. Forced vital capacity,  $FEV_1$ , peak expiratory flow and mid-expiratory values have all been shown to be useful for following the 20 effect of respiratory therapy. (Quakenboss et al., "The Normal Range of Diurnal Changes in Peak Expiratory Flow Rates: Relationship to Symptoms and Respiratory Disease," *Am Rev Resp Dis* (1991) 143, 323-30; Nowak et al., "Comparison of Peak Expiratory Flow and  $FEV_1$ : 25 Admission Criteria for Acute Bronchial Asthma," *Annals of Emergency Medicine* (1982) 11, 64-9.) Because spirometry involves recording several parameters with sensitive and complex instrumentation, the peak expiratory flow rate (PEFR) has been adopted as a useful index for 30 inexpensively allowing patients to monitor their own pulmonary function at home. (Darman, "Pulmonary Function Testing; Use of the Peak Expiratory Flow Rate in an Outpatient or Office Setting," *Journal of Asthma* (1984) 21 (5), 331-37.) The use of objective assessment of 35 pulmonary function for managing asthmatic patients is

critical because patients and physicians tend to inaccurately assess the patients' own pulmonary conditions. (Shim et al., "Evaluation of Severity of Asthma: Patients versus Physicians," *American Journal of Medicine* (68), 11-13.) The inability of patients and physicians to recognize the signs of a severe asthma attack may be a factor contributing to the observed increasing asthma death rates. (Sears, "Increasing Asthma Mortality - Fact or Artifact?," *Journal of Allergy and Clinical Immunology* (1988) 82, 957-60.) Providing patients with peak expiratory flow measurement information may cause them to manage their own asthma more rationally. (Janson, Bjerkel et al., "Effect of Peak Flow Information on Patterns of Self-Care in Adult 15 Asthma," *Heart Lung* (1988) 17, 543-49; Williams et al., "Expiratory Flow Rates: Their Role in Asthma Therapy," *Hospital Practice* (1982) 10, 95-110.)

A rational program for self-administration of aerosolized asthma therapeutic drugs would include: 20 a) avoidance of overuse of bronchodilators, given that all bronchodilator drugs may be potentially toxic when used in excess (W. Spitter et al., "The Use of B-Agonists and the Risk of Death and Near Death from Asthma," *N Engl J Med* (1992) 326, 501-6); and b) using anti-inflammatory 25 drug on a prescribed scale which may include regular dosing several times a day (J.L. Malo et al., "Four-times-a-day Dosing Frequency Is Better than Twice-a-day Regimen in Subjects Requiring a High-dose Inhaled Steroid, Budesonide, to Control Moderate to Severe 30 Asthma," *Am Rev Respir Dis* (1989) 140, 624-28).

It is a problem with peak expiratory flow rate monitoring that peak expiratory flow rate data is typically interpreted out of context with aerosolized drug dosing events. For example, a marginally acceptable 35 peak expiratory flow rate data point with that peak

expiratory flow rate measurement made one minute following the administration of a bronchodilator has a different meaning than if that same measurement with that same value were made one minute prior to the 5 administration of an aerosolized bronchodilator drug.

It is a problem with peak flow monitoring when used to monitor the long-term therapeutic effect of anti-inflammatories aerosolized asthma therapeutic drugs that peak flow data must be interpreted in the context of 10 aerosolized anti-inflammatory drug dosing events. For example, if the patient's peak expiratory flow rate is deteriorating over a period of weeks when the patient is compliant with his anti-inflammatory aerosolized drug 15 therapy program, this deterioration in objective lung function measurement has a very different meaning than if the patient is failing to take his medication as prescribed.

It is a problem with metered dose inhalers that the patient must record in his diary the time of each 20 drug dosing event. It is a problem with portable peak expiratory flow rate measuring devices that the patient must record each peak flow measurement in a diary. There is a system available allowing metered drug dose inhaler drug dosing events to be automatically recorded.

25 (Nebulizer Chronolog.) There is also an instrument available for printing out the time and value of a peak flow measurement made by a patient at home. It is a problem with these automatic dose logging devices and automatic peak expiratory flow rate logging devices that 30 they do not intercommunicate to allow a definitive analysis of the relationship between drug dosing events and peak flow measurement events. In particular, small differences in the real time clocks contained within the dose logging device and peak flow logging device would 35 make it impossible to determine the temporal relationship

of drug dosing events and peak flow monitoring events. When acutely acting bronchodilators are used, a difference of even one or two minutes between the time-based standards used by the drug dosing logging device and the peak flow measurement logging device would introduce unacceptable error in evaluating the relationship of drug dosing and objective pulmonary function measuring events.

It is a problem with these logging devices that when used to monitor a chronic anti-inflammatory aerosolized drug asthma therapy program, the overall compliance of the patient is not easily evaluated. For efficient evaluation of patients in the office setting, an easy-to-read graphical display of long-term compliance with asthma therapy is essential in order to rapidly identify the non-compliant patient and, thus, correctly interpret peak expiratory flow rate data.

#### Summary of the Invention

A method of treating patients suffering from a respiratory disease using a programmable, hand-held, self-contained drug dispensing device is disclosed. The drug dispensing device is comprised of a container which includes a formulation comprised of a respiratory drug such as an anti-inflammatory drug, bronchodilator or enzyme and a suitable propellant which is generally in the form of a low boiling point propellant combined with an excipient which facilitates the suspension of the drug within the propellant. The drug dispensing device is designed such that when the patient withdraws air from a mouthpiece on the device the patient's inspiratory flow is measured and analyzed in terms of liters per minute as well as cumulative inspiratory volume in order to provide an inspiratory flow profile which can be used to

calculate an optimal point for the release of drug from the dispensing device.

A primary object of the invention is to provide a pocket-sized, hand-held, unitary, integrated drug dispensing device designed for the controlled release of respiratory drugs for the treatment of patients suffering from a respiratory disease.

10 A feature of the invention is that the drug dispensing device records the precise date, time and amount of drug released at each dosing event.

Another feature of the present invention is that the device is capable of monitoring pulmonary function.

15 An advantage of the present invention is that the amount and timing of drug released can be cross-referenced with readings on the pulmonary function of the patient in order to provide for means of determining optimal treatment of patients suffering from a respiratory disease.

20 It is another object of this invention to provide a pocket-sized, single, integrated device for recording the date, time and amount of aerosolized drug delivered at each drug delivery event which device is also capable of monitoring pulmonary function and 25 maintaining a record of the date, time and value of each objective lung function.

It is another object of this invention to provide a device capable of monitoring and recording objective pulmonary function information and displaying 30 such information in a manner integrated with drug dosing event information so as to provide a means of evaluating quantitative, objective measures of pulmonary function in the context of actual administered therapy.

35 It is another object of this invention to show that the evaluation of pulmonary function in light of

actual patient compliance only has meaning if drug dosing events are actually associated with patient inspiration and firing of the aerosolized drug into the patient's mouth.

5 It is another object of this invention to show that interpretation of pulmonary function data in the context of actual drug dosing events allows physicians to counsel patients accurately with regard to avoidance of overdosing of potentially toxic inhaled aerosolized  
10 bronchodilators and gives physicians a tool for quantitatively advising patients regarding adjustments to their long-term anti-inflammatory aerosolized drug treatment program and/or long term enzyme treatment program.

15 These and other objects, advantages and features of the present invention will become apparent to those skilled in the art upon reading this disclosure in combination with drawings wherein like numerals refer to like components throughout.

20

#### Brief Description of the Drawings

Figure 1 is a cross-sectional view of a drug delivery device; and

25 Figure 2 is a cross-sectional view of a more preferred embodiment of a drug delivery device.

#### Detailed Description of the Preferred Embodiments

Before the present method of treating patients suffering from a respiratory disease and devices and  
30 formulations used in connection with such are described, it is to be understood that this invention is not limited to the particular methodology, devices and formulations described, as such methods, devices and formulations may, of course, vary. It is also to be understood that the  
35 terminology used herein is for the purpose of describing

particular embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims.

It must be noted that as used herein and in the 5 appended claims, the singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a formulation" includes mixtures of different formulations, reference to "an asthma attack" includes one or more of 10 such events, and reference to "the method of treatment" includes reference to equivalent steps and methods known to those skilled in the art, and so forth.

Unless defined otherwise, all technical and 15 scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the invention, the preferred methods and materials are now 20 described. All publications mentioned herein are incorporated herein by reference to describe and disclose specific information for which the reference was cited in connection with.

The term "respiratory drug" shall be 25 interpreted to mean any pharmaceutically effective compound used in the treatment of any respiratory disease and in particular the treatment of diseases such as asthma, bronchitis, emphysema and cystic fibrosis. Useful "respiratory drugs" include those which are listed 30 within the Physician's Desk Reference. Such drugs include beta adrenergics which include bronchodilators including albuterol, isoproterenol sulfate, metaproterenol sulfate, terbutaline sulfate, and pirbuterol acetate. Anti-inflammatory drugs are often 35 used in connection with the treatment of respiratory

diseases and such drugs include steroids such as beclamethasone dipropionate, triamcinolone acetonide and flunisolide. Other anti-inflammatoryys include cromoglycates such as cromolyn sodium. Other respiratory 5 drugs which would qualify as bronchodilators include anticholenergics including ipratropium bromide. The present invention is intended to encompass the free acids, free bases, salts and various hydrate forms including semi-hydrate forms of such respiratory drugs 10 and is particularly directed towards pharmaceutical acceptable formulations of such drugs which are formulated in combination with pharmaceutically acceptable excipient materials generally known to those skilled in the art.

15 The term "dosing event" shall be interpreted to mean the administration of respiratory drug to a patient in need thereof by the intrapulmonary route of administration which event may encompass one or more releases of respiratory drug formulation from an 20 respiratory drug dispensing device over a period of time of 15 minutes or less, preferably 10 minutes or less, and more preferably 5 minutes or less, during which period multiple inhalations are made by the patient and multiple doses of respiratory drug are released and inhaled. A 25 dosing event shall involve the administration of respiratory drug to the patient in an amount of about 10  $\mu$ g to about 1,000  $\mu$ g in a single dosing event which may involve the release of from about 100  $\mu$ g to about 10,000  $\mu$ g of respiratory drug from the device.

30 The term "monitoring event" shall be interpreted to mean an event taking place prior to a "dosing event" whereby the inspiratory flow of the patient's inhalation is measured in order to determine an optimal inspiratory flow rate and cumulative volume at 35 which to allow the release of a valve so that respiratory

drug can be delivered to the patient. It is preferable to carry out a "monitoring event" prior to each "dosing event" so as to optimize the ability to repeatedly deliver the same amount of respiratory drug to the 5 patient at each dosing event.

The term "inspiratory flow" shall be interpreted to mean a value of airflow calculated based on the speed of the air passing a given point along with the volume of the air passing that point with the volume 10 calculation being based on integration of the flow rate data and assuming atmospheric pressure and temperature in the range of about 18°C to about 30°C.

The term "inspiratory flow profile" shall be interpreted to mean data calculated in one or more 15 monitoring events measuring inspiratory flow rate and cumulative volume which profile can be used to determine a point within a patient's respiratory cycle which is optimal for the release of respiratory drug to the patient. It is emphasized that the optimal point within 20 the respiratory cycle for the release of respiratory drug is not calculated based on a point within the cycle likely to result in the maximum delivery of respiratory drug but rather the point in the cycle most likely to result in the delivery of the same amount of respiratory 25 drug to the patient at each release of respiratory drug from the device.

The terms "lung function" and "pulmonary function" are used interchangeably and shall be interpreted to mean physically measurable operations of a 30 lung including but not limited to (1) inspiratory and (2) expiratory flow rates as well as (3) total lung volume. Methods of quantitatively determining pulmonary function are used to measure lung function. Quantitative 35 determination of pulmonary function is important because lung disease is typically associated with deteriorating

pulmonary function. Methods of measuring pulmonary function most commonly employed in clinical practice involve timed measurement of inspiratory and expiratory maneuvers to measure specific parameters. For example, 5 forced vital capacity (FVC) measures the total volume in liters exhaled by a patient forcefully from a deep initial inspiration. This parameter, when evaluated in conjunction with the forced expired volume in one second (FEV<sub>1</sub>), allows bronchoconstriction to be quantitatively evaluated. A problem with forced vital capacity 10 determination is that the forced vital capacity maneuver (i.e. forced exhalation from maximum inspiration to maximum expiration) is largely technique dependent. In other words, a given patient may produce different FVC 15 values during a sequence of consecutive FVC maneuvers. The FEF 25-75 or forced expiratory flow determined over the mid-portion of a forced exhalation maneuver tends to be less technique dependent than the FVC. Similarly, the FEV<sub>1</sub> tends to be less technique dependent than FVC. In 20 addition to measuring volumes of exhaled air as indices of pulmonary function, the flow in liters per minute measured over differing portions of the expiratory cycle can be useful in determining the status of a patient's 25 pulmonary function. In particular, the peak expiratory flow, taken as the highest air flow rate in liters per minute during a forced maximal exhalation, is well correlated with overall pulmonary function in a patient with asthma and other respiratory diseases.

Each of the indices discussed above is measured 30 during quantitative spirometry. A patient's individual performance can be compared against his personal best data, individual indices can be compared with each other for an individual patient (e.g. FEV<sub>1</sub> divided by FVC, producing a dimensionless index useful in assessing the 35 severity of acute asthma symptoms), or each of these

indices can be compared against an expected value. Expected values for indices derived from quantitative spirometry are calculated as a function of the patient's sex, height, weight and age. For instance, standards 5 exist for the calculation of expected indices and these are frequently reported along with the actual parameters derived for an individual patient during a quantitative spirometry test.

10 The term "respiratory disease" shall be interpreted to mean any pulmonary disease or impairment of lung function. Such diseases can be broadly divided into restrictive and obstructive disease. Restrictive diseases tend to limit the total volume of air that a patient is able to exchange through inspiration and 15 expiration. Restrictive disease, such as can be present in certain types of fibrotic processes, can therefore be detected by reduced FVC indices. Obstructive disease, such as is present in patients with asthma, tends not to affect the total volume of air exchangeable through 20 inspiration and expiration but rather the amount of time required for forced exhalation of air. In particular, the  $FEV_1$  and FVC are markedly reduced in patients with acute asthma symptoms. More specifically, the  $FEV_1$ , when 25 taken as a ratio of FVC (i.e.  $FEV_1$  divided by FVC), is markedly reduced in patients with acute asthma. In addition to increasing the amount of time required for a full forced expiration, the presence of acute 30 bronchoconstrictive disease tends to decrease the peak expiratory flow measured over a typical forced exhalation.

#### General Methodology

35 The invention is the intrapulmonary delivery of respiratory drug to the patient in a controlled and

repeatable manner. The device of the invention provides a number of features which make it possible to achieve the controlled and repeatable dosing procedure required for the treatment of respiratory diseases such as asthma.

5 Specifically, the device is not directly actuated by the patient in the sense that no button is pushed nor valve released by the patient applying physical pressure. On the contrary, the device of the invention provides that the valve releasing respiratory drug is opened

10 automatically upon receipt of a signal from a microprocessor programmed to send a signal when data is received from a monitoring device such as an airflow rate monitoring device. A patient using the device withdraws air from a mouthpiece and the inspiratory rate, and

15 calculated inspiratory volume of the patient is measured one or more times in a monitoring event which determines an optimal point in an inhalation cycle for the release of a dose of respiratory drug. Inspiratory flow is measured and recorded in one or more monitoring events

20 for a given patient in order to develop an inspiratory flow profile for the patient. The recorded information is analyzed by the microprocessor in order to deduce a preferred point within the patient's inspiratory cycle for the release of respiratory drug with the preferred

25 point being calculated based on the most likely point to result in a reproducible delivery event.

The flow rate monitoring device continually sends information to the microprocessor, and when the microprocessor determines that the optimal point in the 30 respiratory cycle is reached, the microprocessor actuates the opening of the valve allowing release of respiratory drug. Accordingly, drug is always delivered at a pre-programmed place in the inspiratory flow profile of the particular patient which is selected specifically to

35 maximize reproducibility of drug delivery and peripheral

deposition of the drug. It is pointed out that the device of the present invention can be used to, and actually does, improve the efficiency of drug delivery. However, this is not the critical feature.

5       The critical feature is the reproducibility of the release of a tightly controlled amount of drug at a particular point in the respiratory cycle so as to assure the delivery of a controlled and repeatable amount of drug to the lungs of each individual patient.

10       The combination of automatic control of the valve release, combined with frequent monitoring events in order to calculate the optimal flow rate and time for the release of respiratory drug, combine to provide a repeatable means of delivering respiratory drug to a 15      patient. Because the valve is released automatically and not manually, it can be predictably and repeatedly opened for the same amount of time each time or for the preprogrammed measured amount of time which is desired at that particular dosing event. Because dosing events are 20      preferably preceded by monitoring events, the amount of respiratory drug released and/or the point in the inspiratory cycle of the release can be readjusted based on the particular condition of the patient. For example, 25      patients suffering from asthma have a certain degree of pulmonary insufficiency which may well change with the administration of drug. These changes will be taken into account in the monitoring event by the microprocessor which will readjust the amount and/or point of release of the respiratory drug in a manner calculated to provide 30      for the administration of an amount of respiratory drug to the patient presently needed by the patient at each dosing event.

35       It has been found that the ability to tightly control the amount of a volatile propellant formulation of drug delivered via the intrapulmonary route can be

improved by delivering smaller doses of the propellant/drug formulation with each release of the valve and with each dosing event. Repeatability, in terms of the amount of respiratory drug delivered to a patient, is improved when the respiratory drug is delivered during a smooth, normal inhalation by the patient. To a certain extent, the ability to provide for a smooth inhalation is enhanced when smaller amounts of respiratory drug are released as compared with larger amounts of respiratory drug. Accordingly, an important aspect of the invention is to deliver aerosolized respiratory drug to a patient in a series of interrupted bursts while the patient continues a single inhaled breath, with each burst being delivered while the patient maintains optimal inspiratory flow.

Short bursts of the release of respiratory drug can be obtained as two or more bursts but are preferably three or four bursts. The amount of time the valve is opened is generally in the range of about 0.05 seconds to 1 second but is more preferably 0.1 seconds to 0.25 seconds. When the respiratory drug is being released in a series of short bursts, it is preferable for the valve to be open a substantially shorter period of time than the valve is closed. For example, the valve might be opened for approximately 0.1 seconds and closed for approximately 0.5 seconds, followed by another opening of 0.1 seconds and another closing of 0.5 seconds, with this pattern being repeated a plurality of times. Repeatability and dosing can be improved by providing for four bursts, wherein each burst allows for the valve to be opened four times, separated by three closings, wherein the amount of closed time is two to eight times longer than the amount of open time for each on/off event. Particularly preferred repeatability can be obtained by allowing for four bursts, wherein the valve

is opened for approximately 0.015 seconds, followed by a closing for approximately 0.1 second, which pattern is repeated for four openings, separated by three closings.

5       The amount of respiratory drug delivered to the patient will vary greatly depending on the particular drug being delivered. In accordance with the present invention it is possible to deliver a wide range of different respiratory drugs with the most preferred drugs being albuterol, beclamethasone dipropionate,

10      10      15      15      15      15      20      20      25      25      30      30

      triamcinolone acetonide, flunisolide, cromolyn sodium, and ipratropium bromide, and include, free acids, bases, salts and various hydrate forms thereof generally administered to a patient in an amount in the range of about 100  $\mu$ g - 10,000  $\mu$ g. These doses are based on the assumption that when interpulmonary delivery methodology is used the efficiency of the delivery is approximately 10% and adjustments in the amount released must be made in order to take into account the efficiency of the device. The differential between the amount of respiratory drug actually released from the device and the amount of respiratory drug actually delivered to the patient varies due to a number of factors. In general, the present device is approximately 20% efficient, however, the efficiency can be as low as 10% and as high as 50% meaning that as little as 10% of the released respiratory drug may actually reach the lungs of the patient and as much as 50% might be delivered. The efficiency of the delivery will vary somewhat from patient to patient and must be taken into account when programming the device for the release of respiratory drug. In general, a conventional metered dose inhaling device is about 10% efficient.

35      When administering respiratory drug using the inhalation device of the present invention, the entire dosing event can involve the administration of anywhere

from 10  $\mu\text{g}$  to 1,000  $\mu\text{g}$ , but more preferably involves the administration of approximately 100  $\mu\text{g}$  to 10,000  $\mu\text{g}$ . The large variation in the amounts which might be delivered are due to the fact that different drugs have greatly 5 different potencies and may be delivered from devices which vary greatly in terms of the efficiency of drug delivered. The entire dosing event may involve several inhalations by the patient with each of the inhalations being provided with multiple bursts of respiratory drug 10 from the device. For example, the device can be programmed so as to release enough respiratory drug so that approximately 1 mg of respiratory drug is delivered to the patient per inhalation or 0.33 mg of respiratory drug per burst with three bursts being delivered per 15 inhalation. If ten mg are to be delivered, the ten mg are delivered by releasing 33 bursts in ten different inhalations. Such a dosing event should take about 1-2 minutes to deliver 10 mg of respiratory drug. Since only small amounts are delivered with each burst and with each 20 inhalation, even a complete failure to deliver respiratory drug with a given inhalation or burst is not of great significance and will not seriously disturb the reproducibility of the dosing event. Further, since relatively small amounts are delivered with each 25 inhalation and/or burst, the patient can safely administer a few additional micrograms (or milligrams for some drugs) of respiratory drug without fear of overdosing.

In addition to drug potency and delivery 30 efficiency, respiratory drug sensitivity must be taken into consideration. The present invention makes it possible to vary dosing over time if asthma sensitivity changes and/or if user compliance and/or lung efficiency changes over time.

Based on the above, it will be understood that the dosing or amount of respiratory drug actually released from the device can be changed based on the most immediately prior monitoring event wherein the 5 inspiratory flow of a patient's inhalation is measured.

Variations in doses are calculated by monitoring the effect of one or more lung function parameters in response to known amounts of respiratory drug released from the device. If the response in 10 changing measured lung function parameters is greater than with previous readings, then the dosage is decreased or the minimum dosing interval is increased. If the response in changing measured lung function parameters is less than with previous readings, then the dosing amount 15 is increased or the minimum dosing interval is decreased. The increases and decreases are gradual and are preferably based on averages (of 10 or more readings of lung function parameter after 10 or more dosing events) and not a single dosing event and monitoring event. The 20 present invention can record dosing events and lung function parameters over time, calculate averages and deduce preferred changes in administration of respiratory drug.

One of the important features and advantages of 25 the present invention is that the microprocessor can be programmed to take two different criteria into consideration with respect to dosing times. Specifically, the microprocessor can be programmed so as to include a minimum time interval between doses i.e. 30 after a given delivery another dose cannot be delivered until a given period of time has passed. Secondly, the timing of the device can be programmed so that it is not possible to exceed the administration of a set maximum amount of drug within a given time. For example, the 35 device could be programmed to prevent dispersing more

than 200 mg of a particular respiratory drug within one hour. More importantly, the device can be programmed to take both criteria into consideration. Thus, the device can be programmed to include a minimum time interval 5 between doses and a maximum amount of drug to be released within a given time period. For example, the microprocessor could be programmed to allow the release of a maximum of 200 mg of a given respiratory drug during an hour which could only be released in amounts of 25 mg 10 with each release being separated by a minimum of five minutes.

The dosing program can be designed with some flexibility. For example, if the patient normally requires 250  $\mu$ g per day of respiratory drug, the 15 microprocessor of the inhalation device can be programmed to provide a warning after 250  $\mu$ g have been administered within a given day and to continue the warning thereafter to alert the user of possible overdoses. By providing a warning and not a lock-out, the device would allow for 20 the patient to administer additional respiratory drug, if needed, due to a decreased lung function and/or account for misdelivery of respiratory drug such as due to coughing or sneezing during an attempted delivery.

The ability to prevent overdosing is a 25 characteristic of the device due to the ability of the device to monitor the amount of respiratory drug released and calculate the approximate amount of respiratory drug delivered to the patient based on monitoring a variety of lung function parameters. The ability of the present 30 device to prevent overdosing is not merely a monitoring system which prevents further manual actuation of a button. As indicated above, the device used in connection with the present invention is not manually actuated, but is fired in response to an electrical 35 signal received from a microprocessor (which received

data from a monitoring device such as a device which monitors inspiratory flow) and allows the actuation of the device upon achieving an optimal point in a inspiratory cycle. When using the present invention, 5 each release of the valve is a release which will administer drug to the patient in that the valve is released in response to patient inhalation. More specifically, the device does not allow for the release of respiratory drug merely by the manual actuation of a 10 button to fire a burst of respiratory drug into the air or a container.

The microprocessor of applicant's invention will also include a timing device. The timing device can be electrically connected with visual display signals as 15 well as audio alarm signals. Using the timing device, the microprocessor can be programmed so as to allow for a visual or audio signal to be sent when the patient would be normally expected to administer respiratory drug. In addition to indicating the time of administration 20 (preferably by audio signal), the device can indicate the amount of respiratory drug which should be administered by providing a visual display. For example, the audio alarm could sound alerting the patient that respiratory drug should be administered. At the same time, the 25 visual display could indicate "50  $\mu$ g" as the amount of respiratory drug to be administered. At this point, a monitoring event could take place. After completion of the monitoring event, administration would proceed and the visual display would continually indicate the 30 remaining amount of respiratory drug which should be administered. After the predetermined dose of 50 mg had been administered, the visual display would indicate that the dosing event had ended. If the patient did not complete the dosing event by administering the stated 35 amount of respiratory drug, the patient would be reminded

of such by the initiation of another audio signal, followed by a visual display instructing the patient to continue administration.

Additional information regarding dosing with 5 respiratory drugs can be found within Harrison's — Principles of Internal Medicine (most recent edition) and the Drug Evaluation Manual, 1993 (AMA—Division of Drugs and Toxicology), both of which are published by McGraw Hill Book Company, New York, incorporated herein by 10 reference to disclose conventional information regarding dosing respiratory drug.

#### Supplemental Treatment Methodology

Patients suffering from a respiratory disease 15 may be treated solely with respiratory drug as indicated above, i.e. by intrapulmonary delivery. However, it is possible to treat such patients with a combination of respiratory drug and other means of administration such as oral administration. The oral drug is preferably 20 given in amount so as to maintain a relatively low level of respiratory drug within the circulatory system which is sufficient to maintain lung function at an acceptable level. However, this low level of drug to blood ratio must be raised in order to improve lung function during 25 periods of respiratory difficulty such as an asthma attack and such can be accomplished by the interpulmonary administration of an respiratory drug using the present invention.

Based on the above, it will be understood by 30 those skilled in the art that a plurality of different treatments and means of administration can be used to treat a single patient. For example, a patient can be simultaneously treated with respiratory drug by transdermal administration, respiratory drug via intrapulmonary administration in accordance with the

present invention, and drugs, which are orally administered.

Delivery Device

5 Before referring to the specific embodiments of the delivery device shown in Figures 1 and 2, an explanation will be provided regarding a general mechanism which can be used in connection with the method of intrapulmonary administration of an respiratory drug.

10 Such a device is a hand held, portable device which is comprised of (a) a means for analyzing the inspiratory flow of a patient and (b) a means for automatically releasing a measured amount of a respiratory drug into the inspiratory flow path of a patient, e.g. an automatic

15 valve actuation means. In order to use the device, the device must be "loaded", i.e. connected to (c) a source of pain relieving drug which, in general, is an respiratory drug such as an anti-inflammatory drug suspension dispersed within a low boiling point

20 propellant. The entire device is light weight (less than 1 kg loaded) and portable.

A formulation of an respiratory drug in a low boiling point propellant is typically contained in a pressurized canister which is connectable to the 25 "unloaded" device, i.e., the device without the container. When the container of propellant and respiratory drug is connected to the device, the container will include a valve opening at one end which opening is seated into a flow path within the device.

30 The device preferably includes a mouth piece at the end of the flow path, and the patient inhales from the mouth piece which causes an inspiratory flow to be measured within the flow path. This inspiratory flow causes an air flow transducer to generate a signal. This signal is 35 conveyed to a microprocessor which is able to convert,

continuously, the signal from the transducer in the inspiratory flow path to a flow rate in liters per minute. The microprocessor can further integrate this continuous air flow rate signal into a representation of 5 cumulative inspiratory volume. At an appropriate point in the inspiratory cycle, the microprocessor can send a signal to an actuation means. When the actuation means is signaled, it releases a valve allowing respiratory drug and propellant to escape into the inspiratory flow 10 path of the device and ultimately into the patient's lungs. After being released, the drug and propellant will preferably pass through a nozzle prior to entering the inspiratory flow path of the device and thereafter 15 the lungs of the patient.

15 It is important to note that the firing threshold of the device is not based on a single criterion such as the rate of air flow through the device or a specific time after the patient begins inhalation. The firing threshold is based on an analysis of the 20 patient's inspiratory flow profile. This means that the microprocessor controlling the device takes into consideration the instantaneous air flow rate as well as the cumulative inspiratory flow volume when it determines the optimal point in the patient's inspiratory cycle 25 which would be most preferable in terms of reproducibly delivering the same amount of drug to the patient with each release of drug. Further, the device preferably includes a means for recording a characterization of the inspiratory flow profile for the patient which is 30 possible by including a microprocessor in combination with a read/write memory means and a flow measurement transducer. By using such devices, it is possible to change the firing threshold at any time in response to an analysis of the patient's inspiratory flow profile, and

it is also possible to record drug dosing events over time.

Figure 1 shows a cross-sectional view of a hand held, portable, electronic breath-actuated inhaler device 5 which can be used in connection with the present invention. The device is shown with a holder 1 having cylindrical side walls and a removable cap. The holder 1 is "loaded" in that it includes the pressurized canister 3. The canister 3 includes a non-metering 10 valve 5 which is held down in the open position when the cap 2 is screwed down, thus setting the valve 5 into a seat 6 which is in connection with a flow path 8.

A formulation 4 comprised of an respiratory drug and a suitable propellant, such as a low boiling 15 point propellant, is contained within the pressurized canister 3. Propellant and respiratory drug are released from the canister 3 via the electrically controlled solenoid 7. In that the valve 5 of the canister is continuously open, another valve, contained within 20 solenoid 7, facilitates the release of the drug. When the solenoid 7 allows release of propellant and drug, the propellant and drug flows through the flow path 8 and then through the solenoid actuated valve 9 into the flow path 10, out through the nozzle 13 and then into the 25 inspiratory flow path 11 surrounded by walls 12.

It is important to note that a variety of devices can be used in order to carry out the respiratory disease treatment methodology of the present invention. However, the device must be capable of allowing the 30 release of a metered amount of respiratory drug based on pre-programmed criteria which are readable by the microprocessor 22. The pre-programmed information is contained within a nonvolatile memory which can be modified via an external device. In another embodiment, 35 this pre-programmed information is contained within a

"read only" memory which can be unplugged from the device and replaced with another memory unit containing different programming information. In yet another embodiment, microprocessor 22, containing read only memory which in turn contains the pre-programmed information, is plugged into the device. For each of these three embodiments, changing the programming of the memory device readable by microprocessor 22 will radically change the behavior of the device by causing microprocessor 22 to be programmed in a different manner. As regards the present invention, the non-volatile memory contains information relevant only to the administration of a specific respiratory drug. Microprocessor 22 sends signals to solenoid 7 which determines the amount of drug delivered into the inspiratory flow path. Further, microprocessor 22 keeps a record of all drug dosing times and amounts using a read/write non-volatile memory which is in turn readable by an external device. The formulation 4 contained within canister 3 is released into the atmosphere ultimately via nozzle 13 which opens into inspiratory flow path 11. It is at this point that the low boiling point propellant within formulation 4 flashes, i.e. rapidly evaporates, thus providing particles of respiratory drug in an aerosol which is introduced into the mouth and ultimately into the lungs of the patient. In order to allow for ease of use, it is possible to form inspiratory flow path 11 into a mouth piece which can be specifically designed to fit the mouth of a particular patient using the device.

The solenoid 7, and associated valve 9, flow paths 8 and 10, as well as nozzle 13 make up the aerosol delivery system 14 shown by the dotted lines within Figure 1. The system 14 is in connection with the flow sensor 15 which is capable of measuring a flow rate of about 0 to about 800 liters per minute. The flow

sensor 15 includes screens 16, 17 and 18 which are positioned approximately 1/4" apart from each other. Tubes 19 and 20 open to the area between the screens 16, 17 and 18 with the tubes 19 and 20 being connected to a conventional differential pressure transducer 21. When the user draws air through inspiratory flow path 11, air is passed through the screens 16, 17 and 18 and the air flow can be measured by the differential air pressure transducer 21. The flow sensor 15 is in connection with the aerosol delivery system 14, and when a threshold value of air flow is reached, the aerosol delivery system 14 allows the release of formulation 4 so that a controlled amount of respiratory drug is delivered to the patient. Solenoid 7 is connected to a microprocessor 22 via an electrical connection. The details of the microprocessor and the details of other drug delivery devices which might be used in connection with the present invention are described and disclosed within US patent application 07/664,758, filed on March 5, 1991 entitled "Delivery of Aerosol Medications for Inspiration" which application is incorporated in its entirety herein by reference, and it is specifically incorporated in order to describe and disclose devices as shown within Figure 1 and the microprocessor and program technology used therewith.

A cross-sectional view of yet another (and more preferred) embodiment of the hand-held, electronic, breath-actuated inhaler device of the invention is shown in Figure 2. The device of Figure 2 shows all of the components present within the single hand held, portable device, i.e. the power source not shown in Figure 1 is shown in the device in Figure 2. Like the device shown within Figure 1, the device of Figure 2 includes a canister 3 which includes a canister valve 5. However, unlike the device of Figure 1, the device of Figure 2

does not have the valve continuously open but allows a valve 5 connected to the canister 3 to be opened by the mechanical force generated by a valve actuation mechanism 26 which is a motor driven, mechanical mechanism 5 powered by a power source such as batteries 23 and 23'. However, like the device shown within Figure 1, the patient inhales through inspiratory flow path 11 which can form a mouth piece in order to obtain a metering event using the differential pressure transducer 21. Further, when the inspiratory flow meets 10 a threshold of a pre-programmed criteria, the microprocessor 24 sends a signal to an actuator release mechanism 25 which actuates the actuation mechanism 26 forcing canister 3 downward so that canister valve 5 releases formulation into the inspiratory flow path 11. 15 Further details regarding the device of Figure 2 are described within co-pending US patent application entitled "An Automatic Aerosol Medication Delivery System and Methods", filed on January 29, 1993 as Serial No. 08/002,507, which application is incorporated herein by reference in its entirety and specifically incorporated 20 in order to describe and disclose devices as shown within Figure 2 and the microprocessor and program technology used therewith.

25 Microprocessor 24 of Figure 2 includes an external non-volatile read/write memory subsystem, peripheral devices to support this memory system, reset circuit, a clock oscillator, a data acquisition subsystem and an LCD annunciator subsystem. The discrete 30 components are conventional parts which have input and output pins configured in a conventional manner with the connections being made in accordance with instructions provided by the device manufacturers. The microprocessor used in connection with the device of the invention is 35 designed and programmed specifically so as to provide

controlled and repeatable amounts of respiratory drug to a patient upon actuation. Adjustments can be made in the program so that when the patient's inspiratory flow profile is changed such is taken into consideration.

5     This can be done by allowing the patient to inhale through the device as a test in order to measure air flow with preferred drug delivery points determined based on the results of several inhalations by each particular patient. This process can be readily repeated when the

10    inspiratory flow profile is changed for whatever reason. When the patient's lung function has decreased the program will automatically back down in terms of the threshold levels required for release of drug. This "back down" function insures drug delivery to a patient

15    in need but with impaired lung function. Determination of optimal drug delivery points in the inspiratory flow can be done at each dosing event, daily, weekly, or with the replacement of a new canister in the device.

20    The microprocessor of the present invention, along with its associated peripheral devices, can be programmed so as to prevent the release of drug from the canister from occurring more than a given number of times within a given period of time. This feature makes it possible to prevent overdosing the patient. The overdose prevention feature can be particularly designed with each individual patient in mind or designed with particular groups of patients in mind. For example, the microprocessor can be programmed so as to prevent the release of more than approximately 200  $\mu\text{g}$  of a given respiratory drug per day when the patient is normally dosed with approximately 100  $\mu\text{g}$  of drug per day. The device can be designed to switch off this lock-out function so that drug can be delivered in an emergency situation.

The systems can also be designed so that only a given amount of a particular respiratory drug is provided at a given dosing event. For example, the system can be designed so that only approximately 10  $\mu$ g of respiratory drug is given in a given 15-minute period over which the patient will make approximately 10 inhalations with 1 mg of drug being delivered with each inhalation. By providing this feature, greater assurances are obtained with respect to delivering the respiratory drug gradually over time and thereby providing relief from the symptoms of respiratory disease without overdosing the patient.

The microprocessor of the invention can be connected to external devices permitting external information to be transferred into the microprocessor of the invention and stored within the non-volatile read/write memory available to the microprocessor. The microprocessor of the invention can then change its drug delivery behavior based on this information transferred from external devices. All of the features of the invention are provided in a portable, programmable, battery-powered, hand-held device for patient use which has a size which compares favorably with existing metered dose inhaler devices.

The microprocessor of the present invention is programmed so as to allow for monitoring and recording data from the inspiratory flow monitor without delivering drug. This is done in order to characterize the patient's inspiratory flow profile in a given number of monitoring events, which monitoring events preferably occur prior to dosing events. After carrying out a monitoring event, the preferred point within the inspiratory cycle for drug delivery can be calculated. This calculated point is a function of measured inspiratory flow rate as well as calculated cumulative inspiratory flow volume. This information is stored and

used to allow activation of the valve when the inhalation cycle is repeated during the dosing event. The devices of Figures 1 and 2 have been put forth in connection with devices which use a low boiling point propellant and 5 preferably use that propellant in combination with a suspension formulation which includes the dry powdered respiratory drug within the low-boiling-point propellant. Those skilled in the art will readily recognize that such devices can be used for administering a solution of 10 respiratory drug within the low-boiling-point propellant. However, those skilled in the art will also readily recognize that different mechanisms will be necessary in order to deliver different formulations, such as a dry powder without any propellant. A device could be readily 15 designed so as to provide for the mechanical movement of a predetermined amount of dry powder to a given area. The dry powder would be concealed by a gate, which gate would be opened in the same manner described above, i.e., it would be opened when a predetermined flow rate level 20 and cumulative volume have been achieved based on an earlier monitoring event. Patient inhalation would then cause the dry powder to form a dry dust cloud and be inhaled. Dry powder can also be aerosolized by compressed gas, and a solution can be aerosolized by a 25 compressed gas released in a similar manner and then inhaled.

The instant invention is shown and described herein in which is considered to be the most practical and preferred embodiments. It is recognized, however, 30 that the departures may be made therefrom which are within the scope of the invention and that obvious modifications will occur to one skilled in the art upon reading this disclosure.

CLAIMS

1. A method of intrapulmonary administration of an respiratory drug, comprising:

5 monitoring lung function of a patient;  
releasing a metered dose of aerosolized respiratory drug from a pressurized canister containing respiratory drug in combination with a low boiling point propellant;

10 inhaling the metered dose of aerosolized respiratory drug into the lungs of a patient;

wherein the releasing is carried out automatically in response to a measured lung function parameters determined by the monitoring and wherein the 15 monitoring and releasing are carried out by a single, hand-held device.

2. The method of claim 1, wherein the releasing, inhaling and monitoring steps are continuously 20 repeated in a manner so as to improve lung function.

3. The method of claim 1, wherein the releasing is automatically carried out by sending an 25 electronic signal to a valve actuation means which opens a valve in response to a received electronic signal.

4. The method of claim 1, wherein the monitoring comprises measuring the inspiratory flow of the patient and calculating an optimal point in an 30 inhalation cycle based on inspiratory flow rate and cumulative inspiratory volume at which the releasing is to take place during a subsequent inhalation.

5. The method of claim 4, further comprising: repeating the measuring, releasing, inhaling and monitoring over a period of time so as to maintain a desired level of lung function parameters as measured by monitoring.

6. The method of claim 1, wherein the respiratory drug is an anti-inflammatory drug.

10 7. The method of claim 1, wherein the respiratory drug is a bronchodilator.

15 8. A method of improving lung function of a patient suffering from a lung disease, comprising: administering respiratory drug to a patient by an intrapulmonary route, the respiratory drug being administered from a hand-held, self-contained device which releases respiratory drug on detecting a threshold level of inspiratory flow created by patient inhalation 20 wherein the threshold level of inspiratory flow required for releasing respiratory drug is a level determined immediately prior to administering respiratory drug.

25 9. The method of claim 8, further comprising: monitoring inspiratory flow of the patient; and repeating the administering and monitoring steps a plurality of times over a period of time so as to maintain a desired level of lung function as measured by monitoring lung function with a self-contained device.

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10. The method as claimed in claim 8, wherein  
the amount of respiratory drug administered and lung  
function monitored are continually recorded and  
adjustments are made in the amount of drug administered  
5 based on the effect of drug administration on the lung  
function of the patient.

11. The method as claimed in claim 8, wherein  
the threshold level of inspiratory flow is determined in  
10 a manner so as to maximize repeatability of the amount of  
respiratory drug delivered to the patient on releasing  
drug.

12. The method as claimed in claim 8, wherein  
15 the respiratory drug is administered in an amount in the  
range of from about 10  $\mu$ g to about 1,000  $\mu$ g.

13. The method as claimed in claim 12, wherein  
the respiratory drug is selected from the group  
20 consisting of anti-inflammatory drugs, bronchodilators,  
enzymes, steroids and anticholinergics.

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14. The method as claimed in claim 8, wherein  
the respiratory drug is selected from the group  
consisting of isoproterenol, cromolyn, albuterol, and  
metaproterenol, terbutaline, pirbuterol, beclamethasone  
5 dipropionate, triamcinolone acetonide, flunisolide, and  
ipratropium bromide, and free acids, bases, salts and  
hydrates thereof.

10 15. The method as claimed in claim 8, further  
comprising:

orally administering a long acting orally  
effective respiratory drug to the patient.

15 16. The method of claim 8, further comprising:  
transdermally administering an respiratory drug  
to the patient.

20 17. The method of claim 16, wherein the  
transdermally administered drug is an anti-inflammatory  
drug.

18. The method of claim 10, further  
comprising:

25 monitoring the inspiratory flow of the patient  
during an inhalation cycle immediately prior to  
administering the respiratory drug and calculating the  
threshold level of inspiratory flow prior to  
administering the drug.

30 19. The method of claim 18, wherein the  
monitoring is carried out immediately prior to each  
dosing event, wherein respiratory drug is administered to  
the patient and wherein the threshold level is a level  
calculated to obtain reproducibility in the amount of

respiratory drug delivered to the patient with each release of drug.

20. A method of improving the lung function of  
5 a patient suffering from a respiratory disease,  
comprising:

10 placing a mouthpiece of a hand-held, metered dose inhaler device in the mouth of a patient, wherein the device is comprised of a container having therein respiratory drug and a low boiling point propellant, a valve for releasing respiratory drug and propellant from the container to the mouthpiece, a means for measuring airflow created by drawing air from the mouthpiece and a means for opening the valve in response to a measured  
15 threshold of airflow;

20 drawing air from the mouthpiece until the threshold is reached so as to cause the valve to open and release a controlled amount of respiratory drug and propellant whereby respiratory drug is drawn into the lungs of the patient, wherein the device includes a microprocessor connected to the means for measuring inspiratory flow and means for opening the valve, the microprocessor being programmed to control the amount of respiratory drug released, based on monitored lung  
25 function of the patient.

21. A device for the intrapulmonary administration of respiratory drug to a patient,  
comprising:

30 a canister containing therein respiratory drug and a low boiling point propellant, wherein the respiratory drug and propellant are held within the canister under pressure;

35 a valve for releasing respiratory drug and propellant from the container;

a channel which allows released respiratory drug to flow from the valve to a mouthpiece which mouthpiece is in fluid connection with the valve;

5 an airflow detecting means capable of detecting inspiratory flow created by a patient inhaling air through the mouthpiece;

10 a microprocessor programmed to receive data from the airflow detecting means and process the data in a manner so as to determine an optimal point within a patient's respiratory cycle for repeatably delivering the same amount of respiratory drug to the patient at which point the microprocessor sends an electrical signal; and

15 an electronic valve actuation means which opens the valve and releases the respiratory drug and propellant from the container upon receipt of the signal from the microprocessor.

22. The device of claim 21, further comprising:

20 a means for recording information including the time during which the valve is open and calculating valve open time in order to determine the amount of respiratory drug released from the container.

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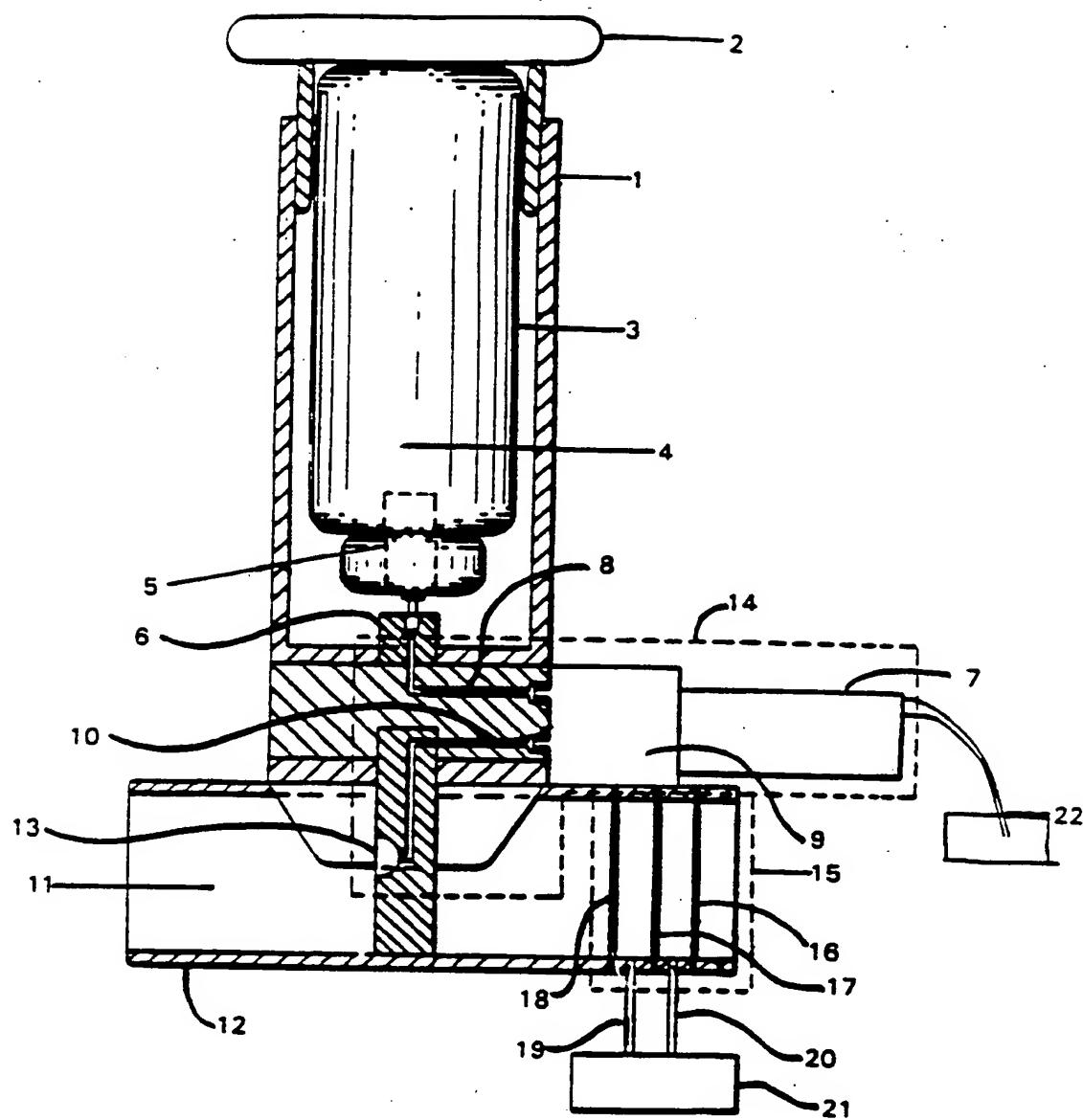


FIG. 1

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2/2

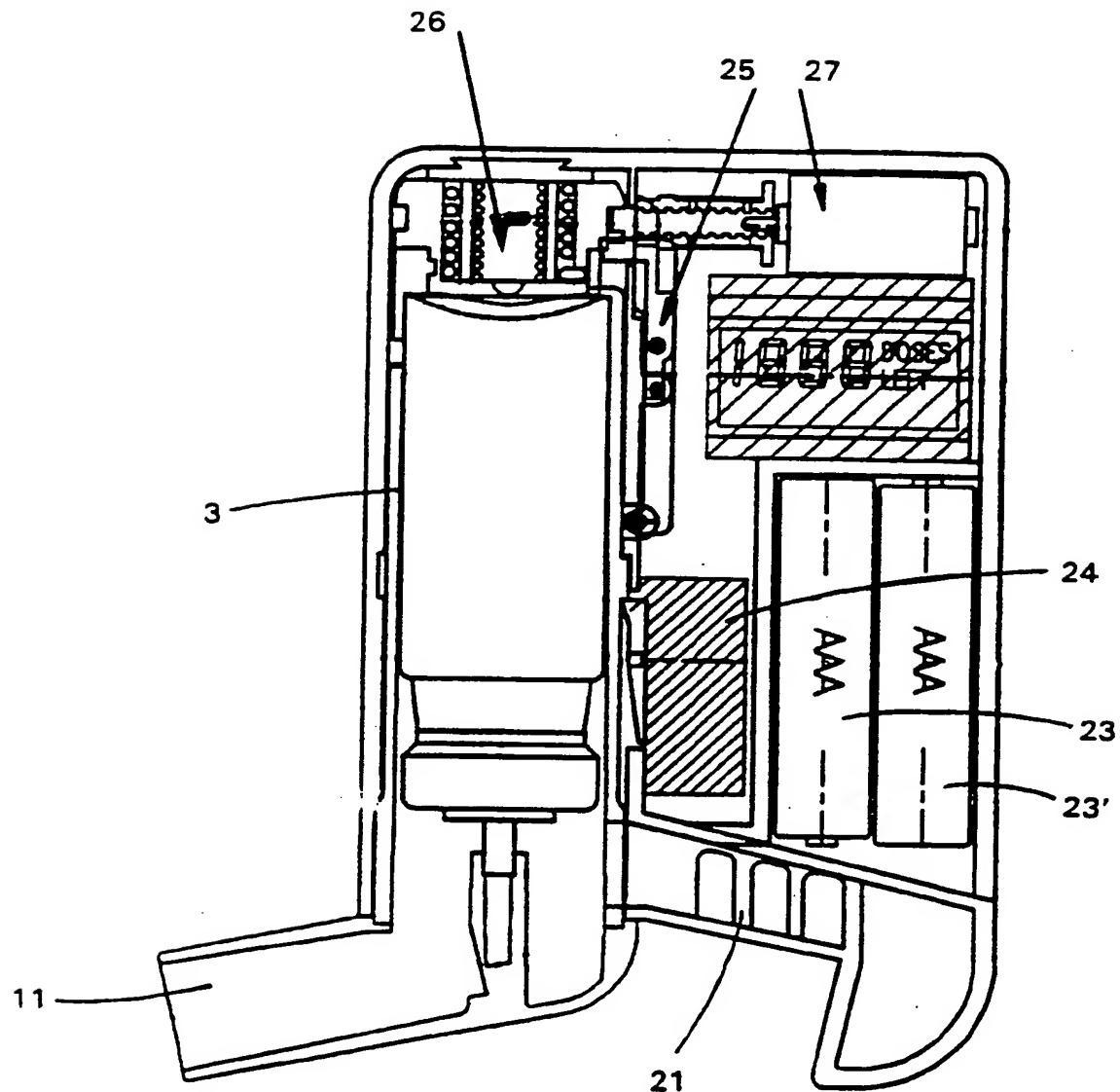


FIG. 2

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## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US94/00992

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) : A61M 11/00, 16/00  
US CL : 128/200.14, 204.21

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 128/200.14, 204.21

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

NONE

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages  | Relevant to claim No. |
|-----------|---|-----------------------|
| Y         | EUR. J. RESPIR. DIS., 62, 3-21, 1981, "HOW SHOULD A PRESSURIZED BETA ADRENERGIC BRONCHODILATOR BE INHALED?", NEWMAN ET AL. SEE FIG. 1 AND PAGE 8. | 1-9, 11-21            |
| Y         | EP 023235 (HOLM) 12 AUGUST 1987, SEE PAGE 4, LINES 9-15 AND PAGE 7, LINES 23-27.  | 10, 22                |

 Further documents are listed in the continuation of Box C. See patent family annex.

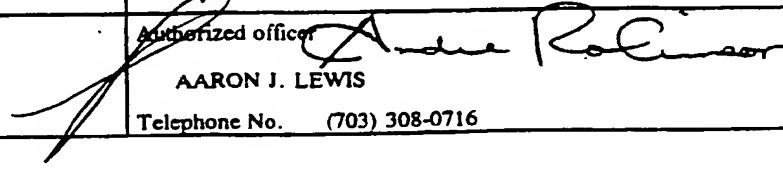
|     |   |     |  |
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| "L" | document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) | "&" | document member of the same patent family  |
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Date of the actual completion of the international search

10 MARCH 1994

Date of mailing of the international search report

15 APR 1994

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